Health Canada Santé Canada

Your health and safety... our priority. *Votre santé et votre sécurité... notre priorité.*

Canadian Adverse Reaction Newsletter

Volume 18 • Issue 2 • April 2008

www.healthcanada.gc.ca/carn

In this Issue

Varenicline and serious psychiatric reactions 1

Serious adverse reaction and medication incident 2

Adverse reaction reporting — 2007 3

Summary of advisories 4

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk-benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

Did you know?

To receive the Newsletter and health product advisories free by email, subscribe to the MedEffect e-Notice at www.healthcanada.gc.ca/medeffect

Varenicline (Champix) and serious psychiatric reactions

Varenicline tartrate (Champix) has been marketed in Canada since April 2007 and is indicated for smoking-cessation treatment in adults in conjunction with smoking-cessation counselling.[1] The efficacy of varenicline in smoking cessation is believed to be a result of the drug's partial agonist activity at the $\alpha 4\beta 2$ nicotinic acetylcholine receptor. By binding to these receptors, varenicline induces 2 results.[2] First, it signals the release of dopamine and creates similar reinforcing effects, but not to the full extent that nicotine does because of its partial binding of the receptor.[2] Second, it acts as a physical antagonist by

Table 1: Summary of reports of aggression, depression and suicidal tendency suspected of being associated with varenicline submitted to Health Canada from Apr. 1, 2007, to Nov. 23, 2007*

Case	Patient age/sex	History of psychiatric condition	Adverse reaction(s)†	Time to onset of reaction, d‡	Outcome after discontinuation of varenicline
1	51/F	No	Aggressiveness	4	Unknown
2	65/M	Yes	Aggressiveness	36	Recovered
3	46/M	Yes	Depression	1	Recovered
4	55/F	Unknown	Depression	≤ 2	Recovered
5	64/M	No	Depression	2	Recovered
6	NA/F	Yes	Depression	≤ 42	NA§
7	64/F	Unknown	Depression	Unknown	NA¶
8	33/F	No	Suicidal tendency	11	Unknown
9	55/F	Unknown	Suicidal tendency	≤ 14	Unknown
10	53/F	No**	Suicidal tendency/ depression	≤ 29	Recovered
11	30/F	Unknown	Suicidal tendency/ depression	≤ 31	Unknown
12	46/M	No	Suicidal tendency/ depression	≤ 32	Recovered
13	54/M	No	Suicidal tendency/ depression	≤ 72	Recovered
14	58/F	Yes	Suicidal tendency/ depression/anger	≤ 13	Recovered

Note: NA = not available.
*These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
†Terms are listed according to the *World Health Organization Adverse Reaction Terminology* (WHOART).
‡Estimated from the beginning of the treatment.
§At the time of reporting, the patient was still taking varenicline and had not yet recovered.
¶The onset of depression was after the discontinuation of the drug.
**Family history of depression was reported.

binding to the nicotine receptor and by blocking the effects of nicotine or a nicotine-replacement agent.[2]

Smoking cessation with or without treatment is associated with various symptoms such as depressed mood, insomnia, irritability, frustration or anger, and anxiety.[1] From Apr. 1 to Nov. 23, 2007, Health Canada received 107 reports of adverse reactions (ARs) suspected of being associated with varenicline. Of these reports, 46 described psychiatric ARs of which 14 reported cases of aggression, depression or suicidal ideation (Table 1). The remaining cases of psychiatric disorders included ARs such as amnesia, abnormal dreams, anxiety, insomnia, abnormal thinking and somnolence.

The impact of a smoking-cessation product with partial nicotinic-receptor agonist properties in patients with underlying psychiatric illness is unknown, and care should be taken with these patients.[1] Two case reports recently described the exacerbation of schizophrenia in one patient[3] and a manic episode in a patient with bipolar disorder taking varenicline.[4]

The Canadian Product Monograph for varenicline was recently revised to indicate that there have been postmarket reports of depressed mood, agitation, changes in behaviour, suicidal ideation and suicide.[1] The product monograph states that not all patients had known pre-existing psychiatric illness and not all had completely discontinued smoking.[1] In November 2007 and February 2008, the US Food and Drug Administration communicated safety notices concerning psychiatric ARs occurring in patients taking varenicline.[5,6] Health Canada is continuing to monitor ARs suspected of being associated with varenicline. Any new safety information on results of analysis will be communicated via the MedEffect e-Notice.

Maria Longo, BScPharm; Tanja Kalajdzic, MSc; Marielle McMorran, BSc, BSc(Pharm), Health Canada

References

1. ***Champix (varenicline tartrate tablets)*** [product monograph]. Kirkland (QC): Pfizer Canada Inc; 2007.
2. Stack NM. Smoking cessation: an overview of treatment options with a focus on varenicline. ***Pharmacotherapy*** 2007;27(11):1550-7.
3. Freedman R. Exacerbation of schizophrenia by varenicline. ***Am J Psychiatry*** 2007;164(8):1269.
4. Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorders. ***Am J Psychiatry*** 2007;164(8): 1269-70.
5. ***Early Communication About an Ongoing Safety Review — Varenicline (marketed as Chantix)***. Rockville (MD): US Food and Drug Administration; 2007 Nov 20. Available: www.fda.gov/medwatch/safety /2007/safety07.htm#Chantix (accessed 2008 Feb 18).
6. ***Information for Healthcare Professions — Varenicline (marketed as Chantix)***. Rockville (MD): US Food and Drug Administration; 2008 Feb 1. Available: www.fda.gov/medwatch /safety/2008/ safety08.htm#Varenicline (accessed 2008 Feb 18).

Serious adverse reaction and medication incident

A 67-year-old woman with a history of metastatic breast cancer that was controlled had cardiomyopathy caused by the chemotherapy, which resulted in ongoing atrial fibrillation and symptoms of congestive heart failure. The patient was taking losartan, metoprolol, warfarin and clodronate. The metoprolol dose was increased and a diuretic added to therapy. The patient's cardiologist later gave her a sample package of long-acting diltiazem (Tiazac) and asked her to come back for follow-up.

The patient took her first dose of diltiazem the following morning and became dizzy and nauseous in the afternoon; she was transported to hospital by ambulance. The emergency physician was unaware that the patient had received a dose of diltiazem because the medication was dispensed as a sample pack and the report from the ambulance attendants was not part of the patient's chart in the treating area. Attempts to gather further information from electronic health records did not indicate that the patient's cancer was controlled. The electronic records did not include information on the diltiazem sample, since they are not designed to capture this type of information. Investigations did not reveal the cause of the rapid onset of the slow heart rate, and therefore the patient was diagnosed with cardiogenic shock due to a poor functioning heart. Given the patient's overall health status, and with no known cause of the rapid deterioration of heart function, a decision to withdraw medical treatment followed, and the patient died.

The concomitant administration of diltiazem with β-adrenergic blocking drugs warrants caution and careful monitoring.[1] Such an association may have an additive effect on heart rate, atrioventricular conduction or blood pressure.[1] In this case, the attending health professionals did not have all the relevant information on the patient's current medications to diagnose a known adverse drug reaction following an interaction between the calcium-channel blocker diltiazem[1] and the β-blocker metoprolol. A recent article on patient safety published by the World Health Organization[2] highlights 2 critical areas relevant to this case

where the potential for medication errors exists: communication gaps during patient handovers and incomplete medication lists at transition in care. Health care professionals are encouraged to report to Health Canada any adverse reactions suspected of being associated with medication incidents.

Marielle McMorran, BSc, BSc(Pharm), Health Canada

References

1. *Tiazac (Diltiazem HCl Extended-Release Capsules)* [product monograph]. Mississauga (ON): Crystaal Corporation; 1997.
2. WHO Collaborating Centre for Patient Safety Releases: nine life-saving patient safety solutions. *Int J Risk Safety Med* 2007;19:171-3.

Adverse reaction reporting — 2007

In 2007, Health Canada received reports of 12 294 new domestic cases of suspected adverse reactions (ARs) to health products (pharmaceuticals, biologics [e.g., fractionated blood products, and therapeutic and diagnostic vaccines], natural health products and radiopharmaceuticals), which were derived from 17 608 reports. The initial report and all subsequent information received as follow-up reports are combined and considered to be one case. The majority of domestic cases were reported by health professionals, either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of cases by reporter type (originator) is outlined in Table 2. In Canada, Market Authorization Holders (MAHs) of health products are required to submit to Health Canada all reports of serious domestic ARs within 15 days of receipt. In addition, MAHs are required to send within 15 days all reports of serious unexpected ARs that have occurred outside Canada (foreign ARs) for the products they sell in other countries as well as in Canada. Of the domestic cases received, 8133 (66.2 %) were classified as serious.*

The reporting of domestic ARs in Canada has increased steadily over the last several years, with 1776 (16.9%) more cases in 2007 than in 2006 (Fig. 1).

Table 1: Source of domestic cases* of adverse reactions (ARs) received by Health Canada in 2006 and 2007

	No. (%) of cases received			
Source	2006		2007	
Manufacturer	6 937	(66.0)	7 573	(61.6)
Canada Vigilance Regional Office	3 370	(32.0)	4 507	(36.7)
Other†	211	(2.0)	214	(1.7)
Total	10 518	(100.0)	12 294	(100.0)

*Cases result from the merge of initial, follow-up and duplicate reports.
†Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of domestic AR cases* by type of reporter (originator) in 2006 and 2007

	No. (%) of cases			
Reporter	2006		2007	
Physician	3 077	(29.2)	3 903	(31.8)
Pharmacist	2 396	(22.8)	2 201	(17.9)
Nurse	806	(7.7)	872	(7.1)
Health professional†	1 281	(12.2)	1 488	(12.1)
Consumer/ patient	2 544	(24.2)	3 592	(29.2)
Other	414	(3.9)	238	(1.9)
Total	10 518	(100.0)	12 294	(100.0)

*Cases result from the merge of initial, follow-up and duplicate reports.
†Type not specified in report.

*In the Food and Drugs Act and Regulations, a serious AR is defined as "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death." A serious unexpected AR is defined as "a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug."

Health Canada also received 258 892 reports of foreign ARs in 2007, a 2.5% increase since 2006 (Fig. 2). At this time, foreign reports are not included in the domestic AR database.

Health Canada would like to thank all who have contributed to the Canada Vigilance Program and encourages the continued support of postmarketing surveillance through AR reporting. To report an AR, go to www.healthcanada.gc.ca/medeffect and:

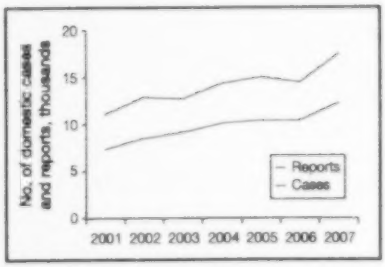

Fig. 1: Number of domestic reports and cases of adverse reactions (ARs) received by Health Canada from 2001 to 2007. (Reports include follow-up, duplicate and unenterable reports. Cases result from the merge of initial, follow-up and duplicate reports.)

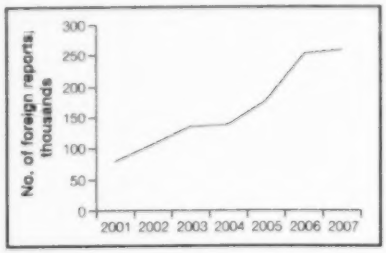

Fig. 2: Number of foreign AR reports received by Health Canada from 2001 to 2007. (Reports include follow-up, duplicate and unenterable reports.)

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined.
Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

- complete and submit a report online, or
- download and print a paper copy of the reporting form and submit it by toll-free fax (866 678-6789) or by mail to one of the Canada Vigilance Regional Offices (addresses are on page 2 of the form).

You can also report an AR by toll-free phone (866 234-2345); calls will automatically be directed to the appropriate Canada Vigilance Regional Office. Incidents involving medical devices are not collected by the Canada Vigilance Program and should be reported toll free through the Inspectorate Hot Line (800 267-9675).

Jennifer Lo, BSc, BA, Health Canada

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Nov. 11, 2007—Feb. 14, 2008)

Date	Product	Subject
Feb 14	Fentanyl	Fentanyl transdermal pain patches recalled due to health risk
Feb 12	Hip implants	Trident hip implants: recall of non-implanted units
Feb 6	Foreign products	Foreign product alerts: Jingzhi Kesou Tanchuan, Guanxin Suhe capsules, Qing Re An Cang Wan, and Guan Xin Su He; Xiao Qin Long Capsules; Xiao Qin Long Wan, Chuan Xiong Cha Tiao Wan Tablets, Bai Tou Weng Wan; Wanniangqing Pai Danggui Niantong Tang; VPX 'No Shotgun' and BSN 'Cell Mass' Body Building Powders; Guipi Wan, Bushen Yijing Wan, Shiquan Dabu Wan, Xiangsha Liujun Wan, Xiaoyao Wan, Vitality Essence Extract Of Deer Fetus, Ptasmin; Yogaraja Guigulu Pills and Pilsol Capsule; Conforer Global Yang Tonic-2; Liang Gel San Concentrated Powder and Qing Xin Lian Zi Yin Concentrated Powder
Jan 28	Foreign products	Foreign product alerts: RGC-RMC Rheumax Capsule; Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules; ZhenZhu HouFengSan Penji, Vyling Cornu Saigae Tatanicae Cooling Tea, Natorny Kwek's Herb 106, Chinese Herbal Heritage Herbal Slimming Tea, Vyling Urticana Itch-Killer A, Vyling Water-Melon Pearls Powder, Phoenix Brand Tea For Sore Throat And Fever, Qing Yin Bai Hua Tea and Yinqiao Flu & Fever Tea
Jan 23	Yeniuyn	Warning: Unauthorized health product contains heavy metals
Jan 7	Foreign products	Foreign product alerts: Santi Bovine Penis Erecting Capsule; Galactogil
Jan 2	Foreign products	Foreign product alerts: Baby's Bliss Gripe Water; Zhong Ti Xiao Er Jian Pi San
Dec 28	Wild Vineyard products	Advisory: unauthorized health products may pose health risks
Dec 28	Magnetic Inductor	Advisory: use of unlicensed Pap-Ion Magnetic Inductor may pose health risk
Dec 21	Ultiva	Recall due to potential for overdose — Abbott Laboratories Ltd.
Dec 21 & 18	Alertec	New warnings regarding serious rash, allergic reactions and mental problems — Shire Canada Inc.
Dec 11	Vaccine	Warning: Three lots of measles, mumps and rubella vaccine suspended
Dec 6	Breast Implants	It's Your Health: Breast implants
Dec 4	Cold and flu	Information update: precautions during cold and flu season
Nov 28	Foreign products	Foreign product alert: Axcil and Desirin
Nov 23	Trasylol	Information concerning safety and availability — Bayer Inc.
Nov 14	Foreign products	Foreign product alerts: Steripaste Medicated Paste Bandages; Royal Medic No.1 Chinese Caterpillar Fungus

Advisories are available at www.healthcanada.gc.ca/medeffect.

Newsletter and Advisories by email

To receive the Newsletter and health product advisories free by email, subscribe to the MedEffect e-Notice at www.healthcanada.gc.ca/medeffect

Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
AL 0701C
Ottawa ON K1A 0K9
Tel: 613 954-6522
Fax: 613 952-7738

Editorial Staff

Ann Sztuke-Fournier, BPharm (Editor-in-Chief)

Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V)

Gilbert Roy, BPharm

Jared Cousins, BSP

Michel Trottier, BScPhm, RPEBC, RPh

Christianne Scott, BPharm, MBA

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

Reporting Adverse Reactions

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

Copyright

© 2008 Her Majesty the Queen in Right of Canada. This publication may be reproduced without permission provided the source is fully acknowledged. The use of this publication for advertising purposes is prohibited. Health Canada does not assume liability for the accuracy of authenticity of the information submitted in case reports.

ISSN 1499-9447, Cat no H42-4/1-18-2E

Aussi disponible en français

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

- complete and submit a report online, or
- download and print a paper copy of the reporting form and submit it by toll-free fax (866 678-6789) or by mail to one of the Canada Vigilance Regional Offices (addresses are on page 2 of the form).

You can also report an AR by toll-free phone (866 234-2345); calls will automatically be directed to the appropriate Canada Vigilance Regional Office. Incidents involving medical devices are not collected by the Canada Vigilance Program and should be reported toll free through the Inspectorate Hot Line (800 267-9675).

Jennifer Lo, BSc, BA, Health Canada

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Nov. 11, 2007—Feb. 14, 2008)

Date	Product	Subject
Feb 14	Fentanyl	Fentanyl transdermal pain patches recalled due to health risk
Feb 12	Hip implants	Trident hip implants: recall of non-implanted units
Feb 6	Foreign products	Foreign product alerts: Jingzhi Kesou Tanchuan, Guanxin Suhe capsules, Qing Re An Cang Wan, and Guan Xin Su He; Xiao Qin Long Capsules; Xiao Qin Long Wan, Chuan Xiong Cha Tiao Wan Tablets, Bai Tou Weng Wan; Wannianqing Pai Danggui Niantong Tang; VPX 'No Shotgun' and BSN 'Cell Mass' Body Building Powders; Guipi Wan, Bushen Yijing Wan, Shiquan Dabu Wan, Xiangsha Liujun Wan, Xiaoyao Wan, Vitality Essence Extract Of Deer Fetus, Plasmin; Yogaraja Guigulu Pills and Pilsol Capsule; Conforer Global Yang Tonic-2; Liang Gel San Concentrated Powder and Qing Xin Lian Zi Yin Concentrated Powder
Jan 28	Foreign products	Foreign product alerts: RGC-RMC Rheumax Capsule; Physio Care Lida Dai Dai Hua Jiao Nang Slimming Capsules; ZhenZhu HouFengSan Penji, Vyling Cornu Saigae Tataricae Cooling Tea, Natorny Kwek's Herb 106, Chinese Herbal Heritage Herbal Slimming Tea, Vyling Urticaria Itch-Killer A, Vyling Water-Melon Pearls Powder, Phoenix Brand Tea For Sore Throat And Fever, Qing Yin Bai Hua Tea and Yinqiao Flu & Fever Tea
Jan 23	Yeniuyn	Warning: Unauthorized health product contains heavy metals
Jan 7	Foreign products	Foreign product alerts: Santi Bovine Penis Erecting Capsule; Galactogil
Jan 2	Foreign products	Foreign product alerts: Baby's Bliss Gripe Water; Zhong Ti Xiao Er Jian Pi San
Dec 28	Wild Vineyard products	Advisory: unauthorized health products may pose health risks
Dec 28	Magnetic Inductor	Advisory: use of unlicensed Pap-Ion Magnetic Inductor may pose health risk
Dec 21	Ultiva	Recall due to potential for overdose — Abbott Laboratories Ltd.
Dec 21 & 18	Alertec	New warnings regarding serious rash, allergic reactions and mental problems — Shire Canada Inc.
Dec 11	Vaccine	Warning: Three lots of measles, mumps and rubella vaccine suspended
Dec 6	Breast Implants	It's Your Health: Breast implants
Dec 4	Cold and flu	Information update: precautions during cold and flu season
Nov 28	Foreign products	Foreign product alert: Axcil and Desirin
Nov 23	Trasylol	Information concerning safety and availability — Bayer Inc.
Nov 14	Foreign products	Foreign product alerts: Steripaste Medicated Paste Bandages; Royal Medic No.1 Chinese Caterpillar Fungus

Advisories are available at www.healthcanada.gc.ca/medeffect.

Newsletter and Advisories by email

To receive the Newsletter and health product advisories free by email, subscribe to the MedEffect e-Notice at www.healthcanada.gc.ca/medeffect

Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
AL 0701C
Ottawa ON K1A 0K9
Tel: 613 954-6522
Fax: 613 952-7738

Editorial Staff

Ann Sztuke-Fournier, BPharm (Editor-in-Chief)

Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V)

Gilbert Roy, BPharm

Jared Cousins, BSP

Michel Trottier, BScPhm, RPEBC, RPh

Christianne Scott, BPharm, MBA

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

Reporting Adverse Reactions

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

Copyright

© 2008 Her Majesty the Queen in Right of Canada. This publication may be reproduced without permission provided the source is fully acknowledged. The use of this publication for advertising purposes is prohibited. Health Canada does not assume liability for the accuracy of authenticity of the information submitted in case reports.

ISSN 1499-9447, Cat no H42-4/1-18-2E

Aussi disponible en français

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.